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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,082	06/20/2007	Jens Fogh	FOGH 5A	4018

1444 7590 03/10/2009

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
03/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,082	FOGH ET AL.	
	Examiner	Art Unit	
	YONG D. PAK	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7-9,11-16,18,24,32,34 and 36-41* is/are pending in the application.

4a) Of the above claim(s) *24,32,34 and 36-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-9,11-16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/12/08&12/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/DK05/00068.

The preliminary amendment filed on June 20, 2007, canceling claims 3-6, 10, 17, 19-23, 25-31, 33, and 35, amending claims 7-9, 11, 13, 15-16, 18, 24, 32, and 34 and adding claims 36-41, has been entered.

The preliminary amendment filed on December 13, 2007, amending claim 1, has been entered.

Claims 1-2, 7-9, 11-16, 18, 24, 32, 34, and 36-41 are pending. Claims 24, 32, 34, and 36-41 are withdrawn. Claims 1-2, 7-9, 11-16, and 18 are under consideration.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-2, 7-9, 11-16, and 18) in the reply filed on December 17, 2008 is acknowledged.

Claims 1-2, 7-9, 11-16, and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 17, 2008.

Claim for Foreign Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on October 2, 2003 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

Claim 1 is objected due to the recitation of "rhASA". Abbreviation/acronym unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation/acronym is used.

Claim 1 is also objected due to the recitation of "sulphatase A". The rest of the claims recite "sulfatase A". In order to achieve uniformity amongst the claims, it is suggested that claim 1 be amended to recite "sulfatase A".

Claims 1-2, 7, and 11 are objected due missing conjunctions between elements i) and ii) in claim 1, (a)-(c) in claims 2 and 7, and II)-VIII) in claim 11.

Claim 18 is objected due to recitation of "Ii".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the phrase "filtration of the sample as performed in step VI of the purification process is replaced by or combined with contacting the sample with a detergent, preferably prior to step V or preferably prior to step Ii of the purification process". It is unclear to the Examiner how the filtration of step "VI" can be combined/replaced with a detergent prior to step "V" or "II". Therefore, the method lacks essential step(s).

For examination purposes, the examiner has interpreted the above phrase as combining any step with contacting rhASA with a detergent. However, if applicants' intended meaning of the phrase is different from the examiner's interpretations as stated above, applicants are requested to so state and clarify the record.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 7-9, 11-16, and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-2, 7-9, 11-16, and 18 are drawn to a method for production of recombinant (A) arylsulfatase A or (B) portions of SEQ ID NO:2 or 3 that are enzymatically equivalent to recombinant human arylsulfatase A.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the examiner has broadly the claims to encompass a method for production of any or all recombinant arylsulfatase A, including any or all mutants, variants and fragments thereof, and any polypeptides comprising a portion of SEQ ID NO:2 or 3 (as little as two amino acids), wherein said polypeptides have arylsulfatase A activity. Therefore, the claims are drawn to a method of producing a genus of polypeptides having arylsulfatase activity but having unknown structure.

In *University of Calfornia v. Eli Lilly & Co.,* 43 USPQZd 1938, the Court of Appeals for the Federal Circuit has held that “A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in

possession of the claimed genus. In addition, MPEP 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The recitation of "arylsulfatase A" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in UC California v. Eli Lilly, (43 USPQ2d 1398) stated that: "in claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed genus of "arylsulfatase A" proteins, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

Therefore, in the instant case, the claim is drawn to a method of producing a genus of polypeptides having arylsulfatase activity but having unknown structure. The specification only describes a method of producing the arylsulfatase A comprising the amino acid sequence of SEQ ID NO:2 or it's fragment, SEQ ID NO:3. While MPEP 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In view of the widely variant species encompassed by the genus, this one example is not enough and does not constitute a representative number of species to describe a method for production of the whole genus comprising any or all recombinant arylsulfatase A, including any or all mutants, variants and fragments thereof, and any polypeptides comprising a portion of SEQ ID NO:2 or 3 (as little as two amino acids), wherein said polypeptides have arylsulfatase A activity, and there is no evidence on the record of the relationship between the structure of the arylsulfatase A of SEQ ID NO:2 and 3 and the structure of any or all recombinant, variant and mutant of any or all polypeptides having arylsulfatase A activity. Therefore, the specification fails to describe a representative species of the genus comprising any or all polypeptides having arylsulfatase A activity.

Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-2, 7-9, 11-16, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing the arylsulfatase A comprising the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3, does not reasonably provide enablement for a method of producing polypeptides having arylsulfatase A activity but having known structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-2, 7-9, 11-16, and 18 are drawn to a method for production of recombinant (A) arylsulfatase A, (B) portions of SEQ ID NO:2 or 3 that are enzymatically equivalent to recombinant human arylsulfatase A or (C) amino acid

analogue having at least 75% sequence identity to (B) or SEQ ID NO:2 or 3 that are enzymatically equivalent to recombinant human arylsulfatase A.

The breadth of the claims.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." In this case, the examiner has broadly the claims to encompass a method for production of (A) any or all recombinant arylsulfatase A, including any or all mutants, variants and fragments thereof, (B) any polypeptides comprising a portion of SEQ ID NO:2 or 3 (as little as two amino acids), wherein said polypeptides have arylsulfatase A activity or (C)polypeptides having at least 75% sequence identity to the polypeptides of (B) or SEQ ID NO:2 or 3, wherein said polypeptides have arylsulfatase A activity. Therefore, the claims are drawn to a method of producing polypeptides having arylsulfatase activity but having unknown structure. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides having arylsultase A activity. In the instant case, the specification enables only a method of producing the arylsulfatase A comprising the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3.

The state of prior art, the relative skill of those in the art, and predictability or unpredictability of the art.

Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's

amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. In addition, the art does not provide any teaching or guidance as to (1) which amino acids within a arylsulfatase A can be modified and which ones are conserved such that one of skill in the art can make the recited polypeptides having the same biological activity as that of the polypeptide of SEQ ID NO:2 or 3, (2) which segments of arylsulfatase A are essential for activity, and (3) the general tolerance of arylsulfatase A to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions.

The amount of direction or guidance presented and the existence of working examples.

The specification discloses a method of producing the arylsulfatase A comprising the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3. However, the speciation fails to provide any information as to (1) specific substrates associated with any arylsulfatase A isolated from any source, including variants, mutants and recombinants thereof, (2) structural elements required in a polypeptide having arylsulfatase A activity, or (3) which are the structural elements in a arylsulfatase A that are essential to display arylsulfatase A activity. No correlation between structure and function of having arylsulfatase A activity has been presented. There is no information or guidance as to which amino acid residues in the polypeptides of SEQ ID NO:2 or 3 can be modified and which ones are to be conserved to create a polypeptide displaying the same activity as that of the polypeptides of SEQ ID NO:2 or 3.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification.

While enzyme isolation techniques, recombinant and mutagenesis techniques were known in the art at the time of the invention, e.g. hybridization or mutagenesis, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect

any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Furthermore, it is not routine in the art to create variants of polynucleotides encoding polypeptides having the activity recited without any knowledge as to the structural features which would correlate with that activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly a method for production of polypeptides having arylsulfatase A activity but having unknown structure. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any or all mutants, variants and recombinants of any or all polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 7-9, 11-16, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Fogh et al.

Claims 1-2, 7-9, 11-16, and 18 are drawn to a method for production of recombinant a recombinant human arylsulfatase A (rhASA) by culturing a human cell producing rhASA in a system comprising a bio-reactor by concentrating the rhASA by tangential flow filtration, using a DEAE sepharose column, using hydrophobic interaction column, using tangential flow filtration, using a polishing step comprising cation and anion exchange columns, using a viral reduction filter, formulating the rhASA in a buffer which comprises using a detergent, and filling the rhASA into a container and freeze-drying the enzyme.

Fogh et al. (WO 02/098455 A2 – form PTO-1449) discloses a method for production of recombinant a recombinant human arylsulfatase A (rhASA) having 100% sequence identity to SEQ ID NO:2 or 3 of the instant invention by culturing a human cell producing rhASA in a system comprising a bio-reactor by concentrating the rhASA by tangential flow filtration, using a DEAE sepharose column, using hydrophobic interaction column, using tangential flow filtration, using a polishing step comprising cation and anion exchange columns, using a viral reduction filter, formulating the rhASA in a buffer which comprises using a detergent (tween 80), and filling the rhASA into a container and freeze-drying the enzyme (pages 14-16 and 40-44 and Sequence Listing pages 1-3). Therefore, the reference of Fogh et al. anticipates claims 1-2, 7-9, 11-16, and 18.

Conclusion

Claims 1-2, 7-9, 11-16, and 18 are rejected.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652